

REMARKS

I. Status of the Claims

Claims 17, 18, 21-23, and 34-37 are pending. Claims 1-16 and 24-33 were previously cancelled. Applicant has amended claims 17 and 18 by deleting “a fragment C and a fraction of fragment B having 11 amino acid residues (amino acids 854-1315 of the tetanus toxin holotoxin)” and inserting “SEQ ID NO: 2.” Support for these amendments includes Figure 1. Applicant has amended claim 36 to correct a minor typographical error. Applicant has also added new claims 38 and 39. Support for these amendments can be found throughout the specification, including at p. 11, lines 5-8, and p. 12, lines 7-17. These amendments do not add new matter.

II. Rejections under 35 U.S.C. § 112, second paragraph

A. The phrase “an associated protein” does not render the claims indefinite

The Office rejects claims 17, 18, 21-23, and 34-37 under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. Office Action, p. 2. According to the Office, “[i]t is unclear as to the metes and bounds of what could be considered ‘an associated protein.’” *Id.* The Office also asserts that “the specification fails to specifically define the phrase ‘an associated protein.’” *Id.*

Applicant respectfully traverses. The claims inform the skilled artisan of their scope when viewed with respect to the disclosure of the specification and the general knowledge in the prior art. See M.P.E.P. § 2173.02. The specification states that “[s]everal molecules can be associated with the TT fragment.” Specification, p. 11, lines 5-6. Immediately following that sentence, the specification states “[i]n association means an association obtained by genetic recombination.” Specification, p. 11, lines 7-

8. The specification also states “[a] chemical linkage is considered for a particular embodiment of the invention and comprises the association between the TT fragment and a polynucleotide encoding the molecule of interest[.]” Specification, p. 12, 7-11. The specification refers to “Bioconjugate Techniques” by Greg T. Hermanson in support of methods for making covalent and non-covalent linkages with TT toxin. Specification, p. 12, lines 14-17. Thus, the specification describes several different ways in which the TT molecule could be “in association” with another molecule. Such molecules can include proteins, such as the “proteins of interest” disclosed in the specification. See specification, p. 10, line 1 to page 11, line 5. Therefore, the specification describes several well known methods for associating a protein with the TT molecule, and the skilled artisan would understand the metes and bounds of the claims. Applicant respectfully requests that the Office withdraw the rejection.

B. The phrase “amino acids 854-1315” does not render the claims indefinite

The Office rejects claims 17, 18, 21-23, and 34-37 under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. Office Action, p. 2. According to the Office, the “amino acid sequence and numbering of the sequence can vary depending on the source of the tetanus toxin holotoxin and which tetanus toxin holotoxin is used for reference.” Office Action, p. 3.

Applicant believes that the inclusion of the phrase “amino acids 854-1315” does not render the claims indefinite, as the skilled artisan could readily determine the metes and bounds of the claims with reference to the sequences provided in the specification. Nevertheless, solely in an effort to further prosecution, Applicant has amended claims

17 and 18 by deleting “ a fragment C and a fraction of fragment B having 11 amino acid residues (amino acids 854-1315 of the tetanus toxin holotoxin)” and inserting “SEQ ID NO: 2.” Applicant respectfully requests that the Office withdraw the rejection.

III. Rejections under 35 U.S.C. § 112, first paragraph

C. The phrase “an associated protein” is supported by the specification

The Office rejects claims 17, 18, 21-23, and 34-37 for alleged failure to comply with the written description requirement of 35 U.S.C. § 112, first paragraph. According to the Office, “[t]he specification fails to provide sufficient support for the phrase ‘an associated protein.’” Office Action, p. 3.

Applicant respectfully traverses. “To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention.” M.P.E.P. § 2163. “An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention.” *Id.* (quoting *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997)).

As noted above, the specification states that “[s]everal molecules can be **associated** with the TT fragment.” Specification, p. 11, lines 5-6 (emphasis added). The specification also states that “this invention provides a composition comprising an active molecule **in association** with the hybrid fragment of tetanus toxin (TT) or a variant thereof.” Specification, page 5, lines 12-14 (emphasis added). The specification lists numerous “molecule[s] having biological function” including “**proteins** of interest.”

See specification, p. 10, line 1 to page 11, line 5 (emphasis added). In addition, the specification describes examples of TT toxins in association with the protein β -lactamase. See e.g., Example 2. Thus, the specification describes molecules “in association” with the TT fragment and provides examples of such proteins, which would lead the skilled artisan to conclude that Applicant was in possession of the invention. It is true that the exact phrase “an associated protein” may not appear in the specification. However, “[t]he subject matter of the claim need not be described literally (*i.e.*, using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement.” M.P.E.P. § 2163.02.

The specification clearly describes compositions in which the claimed hybrid tetanus toxin is in association with other molecules, including proteins, and the skilled artisan would conclude that Applicant was in possession of the invention. Applicant respectfully requests that the Office withdraw the rejection.

D. The phrase “consisting of” is supported by the specification

The Office rejects claims 17, 18, 21-23, and 34-37 for alleged failure to comply with the written description requirement of 35 U.S.C. § 112, first paragraph. The Office asserts that the phrase “consisting of” in claims 17 and 18 “is considered new matter.” Office Action, p. 4. With respect to claim 17, the Office contends that “[i]t is apparent that a hybrid fragment of tetanus toxin **comprising** fragment C and fragment B or a fraction thereof of at least 11 amino acid residues is what is intended throughout the whole specification.” *Id.* (emphasis in original). The Office asserts a similar argument against claim 18. *Id.* at 4-5.

Applicant respectfully traverses the rejection. The specification states that “[o]ur TTC fragment (462 amino acids [sic]) represents the amino acids 854-1315 of tetanus holotoxin, i.e. the carboxy-terminal 451 amino acids of the heavy chain, which constitute the fragment C plus 11 amino acids of the heavy chain that immediately precede the amino terminus of the fragment C.” Specification, p. 20, lines 6-11. The specification also describes examples of plasmids that encode a tetanus toxin consisting of a fragment C and a fraction of fragment B having 11 amino acid residues. See Example 1. Therefore, the application describes the claimed subject matter and provides a figure that graphically depicts the claimed hybrid protein. This disclosure clearly satisfies the written description requirement. Thus, while Applicant agrees that the specification supports molecules **comprising** a fragment C and fragment B, the specification also supports nucleic acid sequences that **consist** of fragment C and a fraction of fragment B having 11 amino acid residues. Accordingly, the skilled artisan would conclude the Applicant was in possession of the invention.

Moreover, the Office has not cited any authority for the proposition that an Applicant cannot narrow the scope of the claims during prosecution. The term “consisting of” is a widely-used and accepted transitional phrase, which narrows the scope of the claim. See *e.g.*, M.P.E.P. § 2163. An applicant is entitled to select transitional phrases that define the claim’s scope. *Id.* Applicant respectfully asserts that the claimed subject matter is fully supported by the specification and requests that the Office withdraw the rejection.

IV. Rejections under 35 U.S.C. § 103(a)

E. Claims 17 and 21 are not obvious

The Office rejects claims 17 and 21 under 35 U.S.C. § 103(a) as allegedly obvious over Fishman *et al.*, "Protein delivery to neurons: tetanus toxin compared to its ganglioside binding fragment (fragment C)," Society for Neuroscience, Abstract 673.1, Vol. 22 (1996) ("Fishman") in view of U.S. Patent No. 5,443,966 ("Fairweather"). According to the Office, Fishman "shows that TTX is superior to its ganglioside binding fragment CF in the capacity for neuronal binding and internalization," and "suggests atoxic tetanus proteins containing additional molecular domains as well as CF may be more suitable vectors for linkage with therapeutic proteins and delivery to neurons." Office Action, p. 6. The Office concedes that "Fishman does not teach a hybrid fragment of tetanus toxin consisting of a fragment C and a fraction of fragment B having 11 amino acid residues (amino acids 854-1315 of the tetanus toxin holotoxin)." *Id.*

The Office asserts that Fairweather "teaches construction of expression plasmid pTet18 expressing a polypeptide which comprises 121 residues of B fragment and all 451 carboxy-terminal residues of C fragment of tetanus toxin[.]" *Id.* at 6-7. In arguing that the combination of Fishman and Fairweather was obvious, the Office asserts that "[o]ne of ordinary skill in the art at the time the invention was made would have been motivated to do so in order to produce a hybrid protein that retains much of the capacity of tetanus toxin for binding and transport by neurons as CF but is superior to CF as taught by Fishman with reasonable expectation of success." *Id.* at 7-8.

Applicant respectfully traverses because Fishman and Fairweather provide no apparent reason for modifying them to arrive at the claimed invention. An obviousness

determination requires factual considerations including the scope and content of the prior art, and differences between the claimed invention and the prior art. See *Graham v. John Deere*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966); See also, *KSR International Co. v. Teleflex Inc.*, 85 U.S.P.Q.2d 1385 (2007). Such factors are considered to determine “whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue.” *KSR*, U.S.P.Q.2d at 1396.

The claimed hybrid consists of a fragment C and a fraction of fragment B having 11 amino acid residues. In contrast, the proteins of Fishman and Fairweather do not consist of the recited 11 amino acid residues of fragment B. There was no apparent reason to simultaneously combine Fishman with Fairweather while at the same time modifying the combination so that only 11 amino acids of the B fragment were in the composition. Fishman teaches that full-length TTX is superior to fragment C (see abstract). In other words, Fishman teaches that inclusion of substantially more tetanus toxin sequence is beneficial. Fishman does not teach or suggest that non-tetanus toxin sequence provided the superior result, and Fishman did not test hybrid proteins.

Similarly, Fairweather uses a composition comprising substantially more tetanus toxin protein, 121 amino acids of fragment B, and neither Fishman nor Fairweather provide any reason for making a composition consisting of a fragment C and a fraction of fragment B having only 11 amino acid residues. In fact, both publications suggest that substantially longer sequences are desirable. Accordingly, one of skill in the art would not have an apparent reason to combine Fishman and Fairweather, while simultaneously modifying the 121 amino acid sequence of Fairweather to the 11 amino acid sequence present in the claimed composition. As such, the claimed composition is

not obvious in view of Fishman, Fairweather, or their combination, and Applicant requests that the Office withdraw the rejection.

F. Claim 18 is not obvious

The Office rejects claim 18 under 35 U.S.C. § 103(a) as allegedly obvious over Fishman and Fairweather and in view of Hone-Zell *et al.*, "Functional characterization of the catalytic site of the tetanus toxin light chain using permeabilized adrenal chromaffin cells," FEBS, 336: 175-80 (1993) ("Hone-Zell"). With respect to Fishman and Fairweather, the Office relies on its reasoning discussed above. Regarding Hone-Zell, the Office asserts that "Hone-Zell teaches zinc and the putative zinc-binding domain constitute the active site of tetanus toxin light chain," and that certain mutations abolish its activity. Office Action, p. 8. According to the Office, it would have been obvious to combine Fishman, Fairweather, as discussed above, and the disclosure of Hone-Zell "would make it obvious for one of ordinary skill in the art to remove said zinc-binding domain when generating a tetanus toxin fragment for neuron specific transport." *Id.* at 9.

Applicant respectfully traverses. As discussed above, there was no apparent reason to simultaneously combine Fishman with Fairweather while at the same time modifying the combination so that only 11 amino acids of the B fragment were in the composition. Both Fishman and Fairweather suggest that longer fragments of tetanus toxin are desirable. Accordingly, it was not obvious at the time the invention was made to combine and modify the teachings of Fishman and Fairweather.

Hohne-Zell does not cure the deficiency of Fishman and Fairweather. Hohne-Zell merely describes the catalytic domain of the B fragment. Hohne-Zell does not

describe fusion proteins, and does not suggest the claimed hybrid protein bearing a mutated B fragment. In view of the disclosure of Hohne-Zell, the skilled artisan would have no reason to combine Hohne-Zell with Fishman or Fairweather to produce the claimed hybrid protein. In addition, Hohne-Zell also fails to provide any reason for combining Fishman with Fairweather while at the same time modifying the combination so that only 11 amino acids of the B fragment were in the composition. Thus, there is no apparent reason that the skilled artisan would have modified and combined Fishman, Fairweather, and Hone-Zell, and the claimed composition is not obvious in view of those publications. Accordingly, Applicant respectfully requests that the Office withdraw the rejection.

G. Claims 17, 21, 23, 34, and 35 are not obvious

The Office rejects claim 17, 21, 23, 34, and 35 under 35 U.S.C. § 103(a) as allegedly obvious over Fishman and Fairweather, on the grounds discussed above, and further in view of Mueller *et al.*, "Toxin-mediated transfer and expression of genes in nerve cells," ARO#27890-LS ("Mueller"). According to the Office, "Mueller teaches that tetanus toxin is specific for uptake into neurons and carboxy terminal (C-fragment) of the protein alone is not toxic and is sufficient for internalization and transport (retrograde)." Office Action, p. 10. The Office concludes that it would have been obvious to combine Mueller with Fishman and Fairweather. *Id.*

Applicant respectfully traverses because Applicant disagrees with the Office's understanding of Mueller. Contrary to the Office's assertion that Mueller teaches that "tetanus toxin is specific for uptake into neurons," Mueller concludes "there is no evidence that this process can be made specific through introduction of a receptor-

mediated mechanism.” Abstract. In fact, Mueller tried multiple experiments to attain specific targeting of neurons, but they all failed. For example, Mueller administered reporter DNA, fragment C, and polylysine carrier complex to mice and concluded: “The results of these experiments were completely negative. There was no evidence for receptor-mediated uptake and expression of RSV- β -GAL under any of the conditions.” Muller, p. 9. A second reporter gene also failed: “Again, the results of these experiments were completely negative. There was no evidence for receptor mediated uptake and expression of CAT under any of the conditions.” *Id.* at 10. In fact, Mueller obtained similar results merely by providing liposomes comprising reporter DNA. See Section 4.B.5 on page 8. Therefore, it is difficult to imagine why the skilled artisan would have used fragment C based on Mueller because Mueller obtained similar results in the absence of that protein. Applicant respectfully asserts that Mueller, whether considered alone or in combination with the publications of record, does not render the claimed invention obvious.

H. Claims 17, 21, and 22 are not obvious

The Office rejects claims 17, 21, and 22 under 35 U.S.C. § 103(a) as allegedly obvious over Fishman and Fairweather, on the grounds discussed above, and further in view of Mueller *et al.*, “Toxin-mediated transfer and expression of genes in nerve cells,” ARO#27890-LS (“Mueller”), and WO/9504151 (“Kahn”). The Office asserts that “Kahn teaches construction of a DNA construct comprising a DNA sequence encoding a fusion protein of the formula: TetC-(Z)a-Het, wherein the TetC is the C fragment of tetanus toxin and Het is a heterozygous protein (e.g. abstract).” Office Action, p. 12. The Office concludes that “[o]ne having ordinary skill in the art at the time the invention was made

would have been motivated [to combine Mueller, Fishman, Fairweather, and Kahn] in order to deliver the protein as a vaccine as taught by Kahn or deliver the therapeutic protein to neurons as taught by Mueller and Fishman with reasonable expectation of success." *Id.*

Applicant traverses. As with the other publications relied on by the Office, Kahn, whether alone or combined with the publications of record, fails to render the claimed composition obvious. Kahn describes plasmids for producing C-fragment fusion proteins and states that "it has often been found that fusing two proteins together leads to an incorrectly folded chimaeric protein which no longer retains the properties of the individual components." Kahn, p. 1, lines 12-15. Thus, Kahn emphasizes the unpredictability of the art of making fusion proteins that function properly. In addition, Kahn does not disclose fusion proteins consisting of a fragment C and a fraction of fragment B having 11 amino acid residues. Kahn does not cure the deficiencies of Fishman, Fairweather, and Mueller because it provides no apparent reason for arriving at a hybrid fragment of tetanus toxin consisting of a fragment C and a fraction of fragment B having 11 amino acid residues.

Accordingly, Kahn either alone or combined with the publications of record, does not render the claimed invention obvious, and Applicant respectfully requests that the Office withdraw the rejection.

V. Conclusion

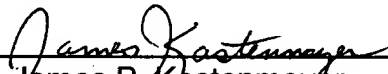
In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

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By: 
James P. Kastenmayer
Reg. No. 51,862
Phone: 202-408-4118
Fax: 202-408-4400
Email: jim.kastenmayer@finnegan.com